UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ASTRAZENECA AB, ASTRAZENECA LP, KBI-E INC., and POZEN INC., Plaintiffs, v. DR. REDDY'S LABORATORIES INC. and DR. REDDY'S LABORATORIES LTD., Defendants.	CIVIL ACTION NO. 11-cv-02317-JAP-DEA (Consolidated for discovery purposes with Civil Action No. 11-cv-04275-JAP-DEA)
ASTRAZENECA AB, ASTRAZENECA LP, KBI-E INC., and POZEN INC., Plaintiffs, v. LUPIN LTD. and LUPIN PHARMACEUTICALS INC., Defendants.	CIVIL ACTION NO. 11-cv-04275-JAP-DEA

DECLARATION OF DR. STEPHEN R. BYRN ON CLAIM CONSTRUCTION

I, STEPHEN R. BYRN, of the City of West Lafayette, State of Indiana, United States of America, **DECLARE AS FOLLOWS:**

A. Educational Background And Qualifications

1. I am the Charles B. Jordan Professor of Medicinal Chemistry in the College of Pharmacy and Pharmacal Sciences, where I have held various professor positions in the areas of pharmaceutical and solid-state chemistry since 1972.

2. I received my Ph.D. in organic and physical chemistry in 1970 from the University of Illinois, after which I was a National Institutes of Health Postdoctoral Fellow for two years at University of California in Los Angeles in the area of physical chemistry. I was Head of the Department of Medicinal Chemistry and Pharmacognosy at Purdue University in the School of Pharmacy and Pharmaceutical Sciences from 1988–1994. I was the Director of the Center for AIDS Research at Purdue from 1988 until 1998. From 1994 to 2009, I was the Head of the Department of Industrial and Physical Pharmacy. I became the Charles B. Jordan Professor of Medicinal Chemistry in 1992.

3. I am co-author of the books "Solid State Chemistry of Drugs," and "Quantitative Pharmaceutical Chemistry." In addition to these books, I have published over 150 articles in peer-reviewed academic journals related to solid-state chemistry, medicinal chemistry, industrial pharmacy, and related areas. I am on the Editorial Advisory Board for the *Journal of Pharmaceutical Sciences*, and have been a member on editorial boards for *Crystal Growth and Design* and *Journal of Pharmaceutical and Biomedical Analysis.* I have also been a reviewer for numerous journals. I am a member of the American Chemical Society, the American Crystallographic Association, and the American Association of Pharmaceutical Scientists.

4. I have acted as a consultant in the pharmaceutical industry both for innovator and generic drugs companies. I have also consulted for the U.S. government. I served as Chair of the Pharmaceutical Sciences Advisory Committee at the FDA from 2000–2001. From 1990 to 2005, I was an Elected Member of the United States Pharmacopeia Revision Committee.

5. I am also founder of SSCI Inc., a problem-solving and analytical contract research laboratory, that specializes in crystallization, stability and polymorphism of pharmaceutical

compounds. SSCI's (now Aptuit Inc.'s) services are performed for both innovator and generic pharmaceutical companies.

6. I have focused on a range of areas in industrial and physical pharmacy, including all aspects of solid state chemistry of pharmaceutical compounds. I consider myself an expert in solid state chemistry, including the analysis of the form, stability, solvates, and polymorphs of drugs. The analysis of solid state chemistry of pharmaceutical compounds employs techniques such as X-ray powder diffraction, solid-state NMR, Raman and infrared spectroscopy; and various methods to determine water content of compounds, such as thermogravimetric analysis, loss on drying, and Karl Fischer titrations. I have personally employed these techniques, and have also supervised extensive use of these techniques.

7. A copy of my curriculum vitae is attached as Exhibit "A."

B. Scope Of Declaration

8. I have been asked by counsel for Plaintiffs AstraZeneca AB; AstraZeneca LP; KBI-E Inc.; and Pozen Inc. ("AstraZeneca") to provide my opinion on the knowledge and understanding of the person of ordinary skill in the art ("skilled person") as related to certain claim language as it appears in the context of U.S. Patent Nos. 6,369,085 (the "'085 patent"); 7,411,070 (the "'070 patent"); and 7,745,466 (the "'466 patent"), including the terms: "the magnesium salt of S-omeprazole trihydrate;" and "a highly crystalline form."

9. Counsel for AstraZeneca has provided me with the following documents, which I have reviewed and considered in providing my opinion stated herein:

(a) U.S. Patent No. 6,369,085 and its prosecution history.

(b) U.S. Patent No. 7,411,070 and its prosecution history.

(c) U.S. Patent No. 7,745,466 and its prosecution history.

(d) Declaration of Dr. Frans Langkilde, dated April 24, 2001.

(e) AstraZeneca's Preliminary Claim Construction Chart and Supporting Evidence.

(f) Defendants' Preliminary Claim Construction Charts and Supporting Evidence.

(g) My own Affidavit submitted in a Canadian proceeding.

(h) The documents cited below.

C. Conclusions

10. In my opinion, the person skilled in the art to whom the '085, '070, and '466 patents are addressed would have a B.Sc. in chemistry or pharmacy, with some knowledge of synthetic or solid state chemistry. The skilled person would also have 3–5 years of experience in the field related to salts, crystallization, preparation, and purification of pharmaceutical compounds. This experience would include analytical techniques used in this field.

11. I have reviewed the whole of the '085, '070, and '466 patents. Counsel has informed me that the claims of the patent define the scope of rights under the patent. The claims must be read from the view of a person skilled in the art. The remainder of the patent document may be used to aid in the understanding of the claims.

12. Counsel has also explained to me the role of the claims in a patent. The claims are intended to define the invention by one or more of its characteristics. Patents typically include several claims, and each claim serves to define the invention or, more precisely, an aspect of the invention. Different aspects of the invention can be defined in different claims. A claim that makes reference to an earlier claim must be read as a definition of an aspect of the invention that includes the definition in the earlier claim as well as at least one additional element.

13. Reading the '085, '070, and '466 patent documents, as a whole, the skilled person would understand that the inventors were for the first time able to make a magnesium salt of S-omeprazole trihydrate. AstraZeneca was also able to characterize example compounds of the magnesium salt of S-omeprazole trihydrate, and show how the magnesium salt of S-omeprazole

trihydrate could be made. The ’070, ’085, and ’466 patents have the exact same specification, description, and figures. The claims of these patents differ in important ways, as I explain below. The ’070 patent is a continuation of the ’085 patent, and has a broader claim 1 than claim l of the ’085 patent. Further, claim 1 of the ’466 is a composition claim which comprises the compound in broader claim 1 of the ’070 patent.

14. Counsel has asked me to comment on the skilled person’s understanding of certain claim language used in the claims of the ’085, ’070, and ’466 patents.

15. In addition to the discussion provided below, I also incorporate and adopt all applicable discussion on the related claims provided in my Affidavit submitted in the Canadian proceeding. (Ex. B).

1. The magnesium salt of S-omeprazole trihydrate

16. The skilled person would understand the phrase “the magnesium salt of S-omeprazole trihydrate,” as it is used in the all of the claims of the’085, ’070, and ’466 patents, has three characteristics, without any additional qualification: a magnesium salt; of the S-omeprazole enantiomer; and a trihydrate. The skilled person would understand “S-omeprazole” to mean the S- or (–)-enantiomer of omeprazole. The term “trihydrate” would, likewise, be readily understood by a person skilled in the art to describe a compound, in theory, having three molecules of bound water per every molecule of the magnesium salt of S-omeprazole (theoretical or stoichiometric ratio). However, in practice it is not necessary for there to be exactly three bound water molecules per every molecule of the salt for the compound to be understood as being a trihydrate.

17. The skilled person would also understand the term hydrate, as used in the term trihydrate, as meaning that the associated water is bound to the molecules of the compound. An example of this is when the drug substance incorporates water into the crystal lattice of its unit cell. (*See* Ex.

C, Byrn, S. et al., *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations, in* Pharmaceutical Research at 945–54 (vol. 12 1995)). A hydrate need not be crystalline to be considered a hydrate, although it must have some structure that can bind water in a regular way. The term hydrate differentiates a compound from other substances in which the water present is loosely associated or only present on the surface. These substances, while they may be measured as having a % water content in a particular hydrate range are not understood to be "hydrates" by the skilled person.

18. Claim 1 of the '070 patent claims the invention of "the magnesium salt of S-omeprazole trihydrate" using exactly those words, without any additional limitations or restrictions to form, crystallinity, purity, or concentration of esomeprazole magnesium trihydrate. Claim 1 of the '466 patent claims "A pharmaceutical composition comprising a first and second active ingredient and a pharmaceutically acceptable, wherein the first active ingredient is the magnesium salt of S-omeprazole . . ." using exactly those words, without any additional limitations or restrictions to form, crystallinity, purity, or concentration of esomeprazole magnesium trihydrate. A person of ordinary skill reading that claim would understand '070 claim 1 and '466 claim 1 to cover esomeprazole magnesium trihydrate of any degree of crystallinity, and to cover esomeprazole magnesium trihydrate in any amount, even if it is mixed with a different form of esomeprazole magnesium. This makes sense, as the magnesium salt of esomeprazole trihydrate in any form or amount was novel at the time of the invention and so no additional restrictions would be necessary to distinguish it from forms of the magnesium salt of S-omeprazole found in the prior art. The declaration of Frans Langkilde makes this expressly clear: "at the time the claimed invention was made, there was no suggestion that the magnesium salt of S-omeprazole existed in a trihydrate form." (*See* Ex. D, AZV00133264–67). Therefore,

"the magnesium salt of esomeprazole trihydrate" is not limited to any form, crystallinity, purity, or concentration of esomeprazole magnesium trihydrate.

19. The skilled person would appreciate the fact that other claims in the patents add limitations and additional requirements to the essential invention, "the magnesium salt of esomeprazole trihydrate." Claim 1 of the '070 patent is not limited by any of the additional requirements of those other claims.

20. The skilled person would understand that Claim 1 of the '085 patent indicates that the structure of the magnesium salt of S-omeprazole trihydrate claimed in that patent, which is otherwise not limited as to form or amount, is determined by examining a list of major peaks in an X-ray diffractogram. In this sense, claim 1 of the '085 patent is narrower than claim 1 of the '070 patent (and the S-omeprazole trihydrate described in claim 1 of the '466 patent). However, claim 1 of the '085 patent is defined by a particular list of x-ray power diffraction peaks, which simplifies the determination of whether a particular sample of magnesium salt of S-omeprazole is the form of esomeprazole magnesium trihydrate covered by claim 1 of the '085 patent. Because of these differences, a skilled person would understand that claim 1 of the '070 patent and claim 1 of the '085 patent cannot be given the same scope.

21. The '085, '070, and '466 patents teach that the magnesium salt of esomeprazole trihydrate can be characterized and identified through the use and combination of several different analytical techniques, including XRPD, FT-IR spectroscopy and Thermogravimetric Analysis (TGA), and by its unit cell. (*See* Ex. E, '085 Pat., col.2 ll.38–41, 58–59; col.3 ll.50–56). In addition to the techniques described in the patent, a person of skilled in the art would also be able to characterize the properties and presence of esomeprazole magnesium trihydrate using a number of techniques, including, but not limited to, single crystal x-ray, all types of

microscopy, calorimetry, Differential Scanning Calorimetry (DSC), Raman spectroscopy, Solid state NMR, IR spectroscopy, laser diffraction, and BET (surface characterization).

22. In trying to understand the scope of the claims of the patents in suit, the skilled person would look first at the claims, and then at the specifications. In looking at the specification, the skilled person would look at the examples as well as the written description to understand the portions of the written description in which the phrases "compound of the invention" and "invention" are used. The skilled person would understand that the inventors used these phrases to describe different example compounds and preferred embodiments as well as some benefits of the product obtained by the claimed processes. (*See, e.g.*, Ex. E, '085 Pat., col. 2 ll.17–59; Ex. F '070 Pat., col.2 ll.22–64; Ex. G, '466 Pat., col.2 ll.19–65). A skilled person would not understand these phrases to limit the scope of every claim. Rather, I am of the view that a person skilled in the art would understand that these sections refer to examples of the magnesium salt of S-omeprazole trihydrate made according to Example 1. This understanding is supported by, for example, the description of FIG. 1 at the beginning of the specification, which describes FIG. 1 as a diffractogram of the esomeprazole magnesium trihydrate prepared according to the "present invention." (Ex. E, '085 Pat., col.1 ll. 55–58). Following this reference to the example of the invention described by FIG. 1, the specification goes on refer to the characteristics of the "compound of the invention." In context, a person of ordinary skill would understand that this is a reference to the characteristics of the preferred example of Example 1 and FIG. 1.

23. This understanding also makes sense when looking at the claims. In this case, several of the characteristics of example compounds are claimed expressly in the claims of the '085 patent and the dependent claims of the '070 and '466 patents. (*See, e.g.*, Ex. E, '085 patent claims 2 and 3; Ex. F, '070 patent claim 2; Ex. G., '466 patent claims 2, 3, 4, and 5). It would make no

sense to require "the magnesium salt of esomeprazole trihydrate" claimed in claim 1 of the '070 patent and claim 1 of the '466 patent to have the purity, crystallinity, and stability characteristics found in a preferred example of the compound obtained by a preferred process.

2. A highly crystalline form

24. The skilled person would understand that the phrase "a highly crystalline form," in the context of claims 2, 4, and 12 of the '085 patent and claims 4 and 12 of the '466 patent, does not require or provide any particular method of measuring or determining crystallinity, nor does it specify a quantity or purity for the compound. While it could be measured using x-ray powder diffraction, it could be measured in other ways.

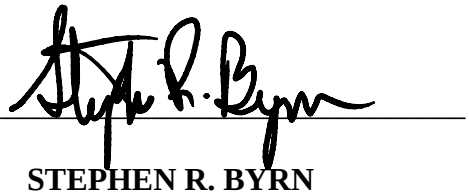
25. In general, the term "crystalline" is readily understood by a person skilled in the art to describe a substance in which the atoms or molecules are arranged in an ordered, repeating pattern. A skilled person reading the specifications of the patent would understand that to be "highly" crystalline, the magnesium salt of S-omeprazole trihydrate has to be more crystalline, or more ordered, than prior art forms of the magnesium salt of S-omeprazole. (*See* Ex. E, '085 Pat., col.3 ll.46–48; Ex. G., '466 Pat., col.2 ll.55–58). However, the skilled person would also understand that the same molecule can exist as a crystal or an amorphous solid, or some mixture thereof, and in an overall substance there may be areas of lower and higher crystallinity or order. Therefore, "highly crystalline" substances, or even "highly crystalline" regions inside of a substance, may be mixed with substances or regions of lower crystallinity, or ones that may be characterized as amorphous. As the '085 and '466 patents do not require or specify a quantity or purity for the "highly crystalline" substance, a skilled person would understand that any amount of "highly crystalline" magnesium salt of S-omeprazole, as detected and characterized by various techniques known in the art, would meet the requirements of the claim. Such a person would

likewise understand that a sample can be characterized as containing "crystalline" material when a mixture of crystalline and amorphous material is present.

26. I reserve the right to prepare exhibits to summarize or support the opinions and bases set forth above. My qualifications and publications are listed in the attached Curriculum Vitae. I have testified as an expert at trial or by deposition in the cases listed at the end of the attached CV. I am being paid $650 per hour for my time spent in study and testimony in this matter.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: May 8, 2012

By: 

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